REMARKS

Claims 1-104 are pending. Claims 105-130 are cancelled pursuant to the restriction requirement, and without prejudice to the prosecution of their subject matter in other patent applications.

The Communication dated December 16, 2004 indicated that the previous Response, submitted on July 8, 2004, by Applicant was not fully responsive, because (i) claims 99-104 were erroneously indicated, in the claim identifier, to be "withdrawn" when they in fact are pending and rejected; and (ii) the text of withdrawn claims was omitted in Applicant's response, when such text must be provided. In this Response, claims 99-104 are correctly identified as original claims, and the text of withdrawn claims is provided. Because the defects noted in the Communication have been corrected, this constitutes a complete response. Therefore, the present response is filed as a substitute to the Response filed July 8, 2004.

Claims 1 and 2 have been amended as discussed below and to place them in proper U.S. form. Claims 5-8 have been amended to correct typographical errors. Withdrawn claims 33-98 have been amended to place them in proper U.S. form. Pursuant to 37 C.F.R. §1.121(c)(2), claims 33-98 are designated with the status identifier "withdrawn - currently amended." The amendments to the claims are supported by the specification and original claims, and do not constitute new matter.

Claims 3-98 are withdrawn from consideration by the Examiner in view of species election requirements. The species election requirements were timely traversed. A Petition for Reconsideration Of Species Election Requirements ("Petition") was also submitted on July 8, 2004. A decision on the Petition mailed November 29, 2004 indicated that the Petition was dismissed as premature, because the restriction requirement has not been made final.

Applicants request that the Examiner reconsider the arguments previously submitted in the responses mailed December 1, 2003 and December 29, 2003. Applicants also present below arguments from the Petition. Should the Examiner remain unpersuaded by the arguments provided in the prior filed responses and the below, Applicants respectfully request that the Examiner make the species election requirement final to permit the reconsideration of the Petition.

Claims 1, 2 and 99-104 are rejected as indefinite and as obvious. For reasons set forth below, Applicant requests that the rejection be removed and that the claims be allowed to issue.

1. The Invention

The present invention, in the broadest sense, is captured by claim 1:

> 1. A topical medicament intended for stopping bleeding, closing a wound, or promoting wound healing in a subject in need of such treatment, comprising the following active agents in therapeutic amounts:
> (i) an agent selected from the group consisting of fibrinogen and fibrin;
> (ii) thrombin;
> (iii) a transglutaminase; and
> (iv) a serpin protease inhibitor which does not inhibit collagenase and elastase;
> wherein the active agents may be obtained from a source selected from the group of allogenic plasma, allogenic tissue, and recombinant production; and
> wherein an active substance of allogenic origin is subjected to a process selected from the group consisting of virus depletion, virus inactivation and a combination thereof; provided that where such a process is applied to the serpin protease inhibitor, it is not applied in the presence of one or more of the other active agents.

Thus, the present invention relates to compositions comprising active agents (i)-(iv), and in addition has four further aspects. First, the source of the four listed active agents may be allogenic plasma or tissue or may be recombinantly produced. Second, an active agent is

subjected to one or more process that depletes and/or inactivates virus. Third, the serpin is a member of this (**ser**ine **p**rotease **in**hibitor) superfamily that does not inhibit collagenase and elastase (so that "the inhibition of proteases released by the granulocytes immigrated into the wound area is largely avoided such that the setting in of wound healing will not be impeded" (in the specification at page 3 line 22 through page 4 line 2)). Fourth, as regards the serpin component, viral depletion/activation is carried out in the absence the other active agents. As to this last feature, the specification states (at page 4 lines 3-10):

> The present invention is further based on the finding that the inhibitory activity of allogenic protease inhibitors will be preserved to a substantially better degree if the latter are subjected to virus inactivation not within a preparation containing one or several of the other active substances of the medicament, but are virus-inactivated separately from the other active substances. In this manner, it is feasible to prepare medicaments according to the invention which contain virus-inactivated allogenic protease inhibitors having sufficient activity so as to inhibit fibrinolytic enzymes in the wound bed after application of the medicament and preventing the detachment of the fibrin wound closure from the wound bed.

Claim 1 is amended to more particularly state the present invention.

2. Restriction Requirement

130 claims were originally filed, directed to (i) topical medicaments (claims 1-104); (ii) a process for preparing a fibrinogen-containing solution (claims 105 and 106); (iii) a medicament comprising a highly purified fibrinogen (claims 107 and 108); (iv) a process for obtaining a pathogen-free active substance (claim 109); (v) a process for covalently binding an active agent to a biological matrix (claim 110): (vi) a process for preparing a fibrin-containing gel (claim 111-116); (vii) a process for solidifying a fibrin-containing gel (claims 117 and 118); (viii) a lyophilized fibrin-containing gel (claims 119 and 120); (ix) a process for preparing a

highly viscous fibrinogen-containing solution (claim 121); (x) a process for determining the adherence of a fibrin clot in a wound bed (claim 122); (xi) a method of treating a wound of a subject (claims 123-130). The Examiner identified twelve separate inventions, one of which is embodied in claims 1-104, which were elected for further prosecution without traverse.

In addition to the restriction requirement, the Examiner issued two species election requirements.

In the first species election requirement, the Examiner required Applicant to select one of the following species: a structural protein (claims 2-5), a cell stimulating factor (claims 5-8), an enzyme or enzyme inhibitor (claims 9-16), an antiadherent, antioxidant or antimicrobial (claims 17-32), a blood coagulation zymogen (claims 33-64) or a particulate cell element (claims 65-95). None of these species is recited in claim 1. Applicant traversed the requirement, but to be responsive elected the species of structural protein.

In the second species election requirement, the Examiner required Applicant to select a species among the species of structural proteins selected. Applicant traversed the requirement, but to be responsive elected the species, allogenic collagen.

In the Official Action dated March 12, 2004, the Examiner rejects Applicant's traversal of the species election requirement, contending:

> [t]he additional components are active ingredients that would materially affect the basic and novel characteristics of the claimed invention. Accordingly, it is proper to consider that searching each and every one of the added active ingredients could entail burden. Burden is established because each of the possible ingredients requires a separate search inasmuch as the different active ingredients are not classified together or recognized in the art as being coextensive.

The Examiner goes on to state:

> Claims 3-98 are withdrawn from further consideration pursuant to 37 C.F.R. 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim (*vide infra*).

Applicant points out that structural proteins (the subject of the first species election requirement), such as allogenic collagen (the subject of the second species election requirement), arise in the claims as a further element -- a **fifth** element – added (by dependent claims) to the composition of claim 1. For example, claim 2 recites:

> 2. The medicament of claim 1, further comprising allogenic collagens subjected to a process selected from the group consisting of virus depletion, virus inactivation, and a combination thereof.

By imposing the species election requirement, the Examiner is ***presupposing*** that claim 1 is not allowable without providing an examination on the merits. The Examiner's contention, that consideration of the dependent claims creates an unreasonable burden to do extensive searching, is not on point. If an independent claim is allowable, there is no need to search the additional subject matter of dependent claims, as dependent claims need not add a separately patentable feature.

Applicant should be given the opportunity to defend the patentability of claim 1 without additional limitations imposed. In the pending official action, claim 1 is rejected, and the Examiner could have properly rejected all its ultimately dependent claims (2-104) as dependent on a rejected claim. To instead withdraw claims 3-98 from consideration is inappropriate. Applicant would further note that if, for the sake or argument only, Applicant added a further element to claim 1 in response to the pending rejection, Applicant would then have the further burden to explain why the addition of that element would obviate the rejection,

relieving the burden placed on the Examiner. If the Examiner believed that the addition of a further element produced too great a burden, he has procedural recourse.

For the foregoing reasons, Applicants respectfully request that the Examiner withdraw the species election requirement. Should the Examiner remain unpersuaded by the arguments provided herein, Applicants request that the Examiner make the species election requirement final to permit the reconsideration of the Petition on its merits.

3. The Claims Are Not Indefinite

Claims 1-2 and 99-104 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for reciting that the active agents "may be obtained." Claim 1, which contains the objected to phrase, has been amended to delete "may be," thereby obviating the basis for the rejection.

Accordingly, it is requested that the rejection be withdrawn.

4. The Claims Are Not Obvious

Claims 1-2 and 99-104 are rejected under 35 U.S.C. §103(a) as being unpatentable over Wadström et al, United States Patent No. 5,631,011 ("Wadström"), Redl et al. , Canadian Patent No. 2302224 ("Redl"), and Edwardson et al., United States Patent No. 5,739,288 ("Edwardson").

According to the Examiner, Wadström discloses:

> fibrin or fibrinogen in a sealant comprising thrombin, transglutaminase, and fibrinolysis inhibitors such as alpha-1 anti-trypsin, PAI-1 or PAI-2, instantly preferred serpins lacking elastase or collagenase activity . . . in combination with additional biofibers such as collagen.

The Examiner acknowledges that Wadström does not teach the use of autologous sources.

According to the Examiner, Redl discloses "a fibrinogen-based adhesive/sealant comprising fibrinogen, thrombin . . . , serum transglutaminase (Factor XIII and a fibrinolysis inhibitor) where the latter preferably is an elastase inhibitor. The Examiner acknowledges that Redl "lacks serpins lacking elastase or collagenase activity as the fibrinolytic inhibitor, autologous sources for the active ingredients or collagen, or fibrin as the other sealant agent."

Finally, Edwardson is said to "disclose the use of non-crosslinked fibrin in a fibrin-based adhesive/sealant" where the blood used to produce the sealant may be autologous, and where "[i]t is also reported that it is known in the art to add fibrinolytic inhibitors such as PAI-1 or PAI-2 (the instantly most preferred serpins) to the fibrin sealant.

The Examiner concludes:

> A person of ordinary skill in the art at the time the invention was made would have been motivated to substitute autologous sources for the active components of the fibrin adhesive/sealant of [Wadström] and [Redl] because [Edwardson discloses] them to be functionally equivalent in a fibrin adhesive or sealant save the well-known advantage of eliminating an immunological reaction. [Wadström] and [Edwardson] both disclose that the fibrinolytic inhibitors are readily selected from a small group that highlights the most preferred serpins of the instant application. Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use autologous active ingredients, fibrin or fibrinogen, or serpins lacking collagenase or elastase activity in a fibrin-based adhesive/sealant.

Applicant respectfully disagrees, and asserts that the claims are not obvious over any of the cited references, taken singly or in combination. As explained in Section 1 of this paper, the claimed invention has a number of requirements, including the presence of active agents (i)-(iv), and four additional aspects, namely the *source* of the active agents (allogenic or recombinant), the step of *viral depletion and/or inactivation*, the *serpin's lack of collagenase and/or elastase activity* and the *separate antiviral treatment of the serpin*.

Neither the cited references nor any combination thereof disclose *or suggest* topical medicaments having the recited four components (fibrinogen or fibrin, thrombin, a transglutaminase, and a serpin) and the four characteristics set forth above.

For example, Wadström has as its primary goal the provision of fibrin-based adhesives that do not suffer from low viscosity, and as such may contain biodegradable/biocompatible polymers. Wadström does not disclose or consider treatment of its compositions to deplete and/or inactivate viruses, nor does it teach, suggest or imply the importance of separate treatment of serpins, or the use of serpins lacking collagenase and elastase activity.

Edwardson mentions the desirability of using autologous sources to reduce the risk of transmission of infection, but does not otherwise teach a virus depletion/inactivation step. Edwardson does not teach the desirability of using serpins lacking collagenase and elastase activity, nor separate viral depletion/inactivation of serpins.

Finally, Redl focuses on the inclusion of an elastase inhibitor. Redl does teach the desirability of viral inactivation, but it does not disclose or suggest the use of serpins lacking collagenase (or arguably elastase) activities nor the separate antiviral treatment of serpin inhibitors.

Accordingly, none of the cited references, nor any combination thereof, teach or suggest all components of the claimed invention, namely a medicament comprising (i) an agent selected from the group consisting of fibrinogen and fibrin; (ii) thrombin; (iii) a transglutaminase; and (iv) a serpin protease inhibitor which does not inhibit collagenase and elastase; wherein an active substance of allogenic origin is subjected to a process selected from the group consisting of virus depletion, virus inactivation and a combination thereof; provided

that where such a process is applied to the serpin protease inhibitor, it is not applied in the presence of one or more of the other active agents. Rather, each of the cited references take a different direction toward improving fibrin adhesives, with the directions being so diverse that they cannot be consider to create any motivation in the skilled artisan to produce the presently claimed invention.

5. Conclusion

For all the foregoing reasons, the pending rejections should be removed. For reasons set forth above, claims 1, 2 and 99-104 are patentable, and claims 3-98 should be considered in the present application and deemed allowable.

Respectfully submitted,
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